SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: *Restylane® Defyne*

Device Procode: LMH

Applicant's Name and Address: Q-Med AB, a Galderma affiliate
Seminariegatan 21
SE-752 28 Uppsala, Sweden

Galderma Research & Development, LLC
14501 North Freeway
Fort Worth, TX 76177

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140029/S027

Date of FDA Notice of Approval: January 29, 2021

The original PMA (P140029) for *Restylane® Refyne* and *Restylane® Defyne* was approved on December 9, 2016. *Restylane® Defyne* is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21. The SSEDs to support these indications are available on the CDRH website and incorporated by reference herein.

The current supplement was submitted to expand the indication for *Restylane® Defyne*. The study was performed in the US under IDE G180063 to establish a reasonable assurance of safety and effectiveness for the use of *Restylane® Defyne* for augmentation of the chin region to improve the chin profile in patients with mild to moderate chin retrusion over the age of 21.

II. INDICATIONS FOR USE

Restylane® Defyne is indicated for injection into the mid-to-deep dermis for correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds) in

patients over the age of 21.

Restylane® Defyne is indicated for injection into the mid-to deep dermis (subcutaneous and/or supraperiosteal) for augmentation of the chin region to improve the chin profile in patients with mild to moderate chin retrusion over the age of 21.

III. CONTRAINDICATIONS

- *Restylane® Defyne* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane® Defyne* may contain trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- *Restylane® Defyne* contains lidocaine and is contraindicated for patients with a history of allergies to such material.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the *Restylane® Defyne* physician labeling.

V. DEVICE DESCRIPTION

Restylane® Defyne is a sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless and homogeneous soft hyaluronic acid gel. *Restylane® Defyne* is crosslinked with BDDE (1.4-butanediol diglycidylether). The product has a sodium hyaluronate concentration of 20 mg/mL in phosphate buffered saline at pH 7 and contains 3 mg/mL lidocaine hydrochloride.

The gel is supplied in a prefilled plastic syringe. The syringe and its contents are steam sterilized. The syringe is individually packaged in a blister, with two 27G x ½" ultra-thin wall (UTW) needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other approved injectable gels and procedures in the United States (US) for augmentation of the chin region to improve the chin profile, such as, fat grafting and implants. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Restylane® Defyne is manufactured by Q-Med AB and was approved for marketing in the European Union in January 2010. In 2016, *Restylane® Defyne* received US marketing approval (P140029) for injection into the mid-to-deep dermis for the correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21. *Restylane® Defyne* has been approved for marketing in over 70 countries. Since introduced, the number of treatments worldwide with *Restylane® Defyne* is estimated at roughly one million. To date, *Restylane® Defyne* has never been removed from the marketplace for any reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Injection site reactions events such as bruising, erythema, itching, swelling, pain, lumps/bumps, discoloration, and tenderness are anticipated and expected to generally resolve spontaneously within one week after injection. Lumps/bumps may last longer, but typically resolve in less than 30 days.

For the specific adverse events that occurred in the clinical study, please see SECTION X.d.

Post-marketing surveillance

The adverse events received from post-marketing surveillance (voluntary reporting and published literature) for the use of *Restylane® Defyne* with and without lidocaine in the US and other countries most commonly included reports of transient swelling/edema with immediate onset or delayed onset, one to three months after treatment.

The following events were also reported in decreasing order of frequency (non-exhaustive list):

- mass formation/induration
- papules/nodules
- erythema
- pain/tenderness
- short duration of effect
- bruising/hematoma
- presumptive bacterial infections and abscess formation
- inflammation
- discoloration
- injection site reactions including burning sensation, irritation and warmth
- ischemia and necrosis due to unintentional intravascular injection or

embolization
- hypersensitivity/angioedema
- granuloma/foreign body reaction
- pruritus
- neurological symptoms including hypoaesthesia, paraesthesia and facial paralysis
- eye disorders such as eye swelling, eye pain, eyelid oedema, eyelid ptosis, blurred vision, ocular discomfort and visual impairment
- rash
- device dislocation
- blisters/vesicles
- symptoms of reactivation of herpes infection
- deformity/assymetry
- discharge
- atrophy/scarring
- urticaria
- capillary disorder such as telangiectasia
- dermatitis
- acne
- extrusion of device
- non-dermatological events including chills, discomfort, dizziness, headache, malaise, nausea and pyrexia and
- other dermatological events including pain of skin

When required, treatments for these events included ice, massage, warm compress, nitroglycerine paste, corticosteroids, antibiotics, antihistamines, analgesics, antiviral agents, diuretic agents, aspiration/incision, drainage, surgery or enzymatic degradation (with hyaluronidase) of the product.

Reports of serious adverse events for *Restylane® Defyne* with and without lidocaine are rare. The most commonly reported serious adverse events were infection/abscess, mass/induration, ischemia/necrosis and eye disorders. Other concurrent serious events included: swelling pain/tenderness, erythema and discoloration.

Serious infection/abscess were mostly reported with a time to onset ranging from one day up to 4 months following the injection. Most of the patients were recovering at the time of last contact. The treatments may include: antibiotics, analgesics, corticosteroids and hyaluronidase.

Serious mass/induration including granuloma/foreign body reaction was mostly reported with a time to onset ranging from a month to 4 months or longer. The outcome was mainly recovered or recovering at the time of last contact. Granuloma is rarely confirmed with histopathological for diagnosis. The treatments may include: analgesics, antihistamine, antibiotics, corticosteroids, excisions, and biopsy.

Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of up to several weeks have been reported. In case of unexplained inflammatory reactions infections should be excluded and treated if necessary since inadequately treated infections may progress into complications such as abscess formation. Treatment using only oral corticosteroids without concurrent antibiotic treatment is not recommended.

Vascular occlusion resulting in ischemia/necrosis and visual disturbances, including blindness, have been reported following facial aesthetic treatments with injectable soft tissue fillers, with a time to onset ranging from immediate to a few weeks following injection. Vascular compromise may occur due to an inadvertent intravascular injection or as a result of local vascular compression by the implant. This may manifest as blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolization.

Isolated rare cases of ischemic events affecting the eye and brain have led lead to vision loss, and cerebral infarction, respectively. Vision abnormalities including blindness have been reported following injection of dermal fillers including HA, with and without lidocaine, into the nose, glabella, periorbital areas, and/or cheek, with a time to onset ranging from immediate to a few days following injection. Treatments may include anticoagulants, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, local vasodilating agents such as PDE-5 inhibitor and nitropaste, antibiotics, drainage, surgery and hyperbaric oxygen. Outcomes ranged from resolved to ongoing at the time of last contact. In many of the events requiring medical intervention the patient was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory studies

There are no manufacturing or specification changes due to this supplement.

B. Biocompatibility studies

This supplement describes clinical data to support approval of a new indication for use. Because no change in product manufacture or specification was proposed, the biocompatibility studies previously presented in PMA P140029 and supplements support the new proposed indication for use.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for the use of *Restylane® Defyne* for augmentation of the chin region to improve the chin profile in patients over the age of 21 in the US under IDE

G180063. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between August 21, 2018 and November 25, 2019. The database for this PMA supplement reflects data collected through February 20, 2020 and included 140 subjects at 11 investigational sites in the US.

The pivotal study was a randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of *Restylane® Defyne* in the chin for augmentation of the chin region to improve the chin profile. A total of 140 subjects were randomized in a 3:1 ratio to treatment with *Restylane® Defyne* or no-treatment.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the clinical study was limited to subjects who met the following key inclusion criteria:

- Willing to comply with the requirements of the study and providing a signed written informed consent
- Males and non-pregnant, non-breastfeeding females, over the age of 21
- Seeking augmentation therapy for chin retrusion
- Grade of 1 (mild) or 2 (moderate) on the Galderma Chin Retrusion Scale (GCRS) as assessed by the Blinded Evaluator.
- Willing to abstain from any other facial plastic surgical or cosmetic procedures for the duration of the study (e.g., laser or chemical resurfacing, facelift, etc.)
- If the subject was a female of childbearing potential, agreed to use an acceptable form of effective birth control
- Negative urinary pregnancy test for females of childbearing potential at screening and all injection visits.

Subjects were not permitted to be enrolled in the clinical study if they met any of the following key exclusion criteria:

- Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram-positive bacterial proteins.
- History of allergy or hypersensitivity to lidocaine or other amide-type anesthetics, or topical anesthetics or nerve blocking agents.
- Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis of angioedema, or family history of these conditions.
- Previous use of any permanent (non-biodegradable) or semi-permanent (e.g., calcium hydroxylapatite or Poly-L-Lactic acid) facial tissue augmentation therapy, lifting threads, permanent implants or autologous fat below the level of the horizontal line from subnasale.

- Previous use of any HA based or collagen based biodegradable facial tissue augmentation therapy in the chin and lips within 12 months prior to the baseline visit.
- History of other facial treatment/procedure in the previous 6 months below the level of the horizontal line from subnasale, that in the Treating Investigator's (TI's) opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation (e.g., facelift, oral surgery, resurfacing, mesotherapy, lipolytic injections, Botulinum toxin injections).
- Previous facial surgery (including facial aesthetic surgery and liposuction) below the level of the horizontal line from subnasale.
- History of cancer or previous radiation near or on the area to be treated.
- Presence of any disease or lesions near or on the area to be treated (e.g., inflammation, active, or chronic infection; facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes simplex or herpes zoster; scars or deformities; cancer or precancer such as actinic keratosis or actinic cheilitis).
- Subjects with temporomandibular joint dysfunction, jaw pain, chewing pain, muscular related pain in the treatment area, and pain from opeing and closing the mouth.
- Presence of tattoo, piercing, beard or facial hair, which in the TI's opinion, would interfere with the study injections and/or study assessments.
- Presence of dental, oral, or facial condition which, in the TI's opinion, would interfere with the study injections and/or study assessment (e.g., dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities).
- Presence of abnormal rating in chin or lower lip sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the chin or the lower lip.
- Presence of abnormal rating in lip movement, which inability to pronounce all pre-selected words.
- Presence of abnormal rating in lip function, with inability to effectively suck water through a straw.
- Detection of any abnormal chin structure, such as a lump/mass formation or non-uniform density.
- An underlying known disease, a surgical or medical condition that would expose the subject to undue risk, e.g. HIV, active hepatitis, autoimmune disease, history of bleeding disorders, connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, or scleroderma.
- Evidence of scar-related disease or delayed healing activity within 1 year prior to the baseline visit.
- Use of concomitant medication that have the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation (e.g., aspirin or other non-steroidal anti-inflammatory drugs [NSAIDs], Omega 3 or Vitamin E), within 14 days prior to injection. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.

- Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies, antiviral treatment for HIV or Hepatitis), systemic corticosteriods (inhaled corticosteroids are allowed) within 3 months prior to Baseline visit.
- Use of topical facial corticosteroids or prescription retinoids (below the level of the horizontal line from subnasale) within 1 month of the Baseline visit or systemic retinoid treatment within 6 months of the Baseline visit.
- Presence of any condition, which in the opinion of the Treating Investigator makes the subject unable to complete the study per protocol (e.g., Subjects not likely to avoid other prohibited facial cosmetic treatments; Subjects not likely to complete the study because of other commitments; Subjects anticipated to be unavailable for visits, incapable of understanding the investigational assessments or having unrealistic expectations of treatment result; Subjects who have a concomitant condition (e.g., acute viral or bacterial infection with fever) that might confuse or confound study treatments or assessments).
- Participation in any interventional clinical study within 30 days of screening.
- Study site personnel, close relatives of the study site personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.

2. Follow-up Schedule

In the pivotal study, qualified subjects were randomized to receive treatment with *Restylane® Defyne* or no-treatment for for augmentation of the chin region to improve the chin profile.

Subjects had scheduled visits at 2 and 4 weeks after treatment at baseline. Optional touch-up treatment for the treated subjects was offered at Week 4 if optional correction was not achieved.

If a touch-up was performed, a second 2-week and 4-week follow-up visit was scheduled.

Subjects had in-clinic follow up visits to evaluate safety and effectiveness at 2, 4, 12, 24, 36, and 48 weeks after the last injection. At the 48-week visit after all study procedures were completed, all subjects, regardless of randomization assignment at baseline, were offered optional treatment with *Restylane® Defyne* if optimal aesthetic improvement was not maintained. If treatment was performed at the 48-week visit, 2, 4, and 12-week follow up visits were scheduled.

Subjects were contacted by telephone 72 hours after each treatment (i.e. initial, touch up, optional retreatment at Week 48, as applicable) for safety follow-up.

Subjects evaluated injection site reactions in a 28-day diary, starting on the day of treatment and at each treatment time point.

The method of injection was at the discretion of the Treating Investigator. A sufficient amount of product was injected to achieve optimal correction of the chin, in the opinion of the Treating Investigator and subject. Optimal appearance was defined as at least 1 GCRS point improvement from baseline and the best correction that could be achieved as agreed by the Treating Investigator and the subject. The maximum recommended injection volume per subject at the initial and re-treatment visits was 4.0 mL, and 2.0 mL at the optional touch-up.

3. Clinical Endpoints

With regards to safety, *Restylane® Defyne* in the chin area was evaluated by: a) the incidence, severity, and duration of predefined, expected post-treatment injection site reactions using a subject diary for 28 days after each treatment and for each treatment area, b) the incidence, severity, duration, and onset of related AEs collected during the study, and c) chin and lower lip safety assessments as evaluated by a qualified study staff member at each visit.

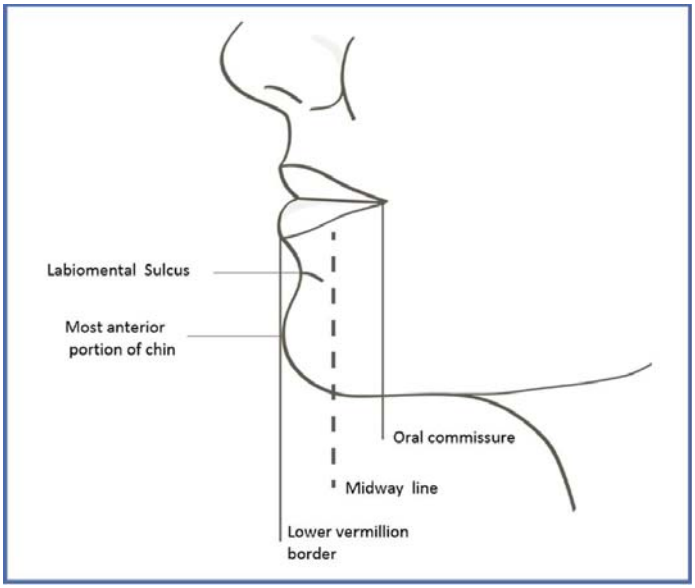
The primary analysis for improvement of chin retrusion was evaluated based on responder rates using the GCRS (ne if randomized to no treatment.

Table 1, Figure 1). Responders were defined as having at least 1 point improvement from baseline (as assessed by the blinded evaluator) at 12 weeks after last injection for the treatment group, or after baseline if randomized to no treatment.

Table 1. Galderma Chin Retrusion Scale (GCRS)

Score	Grade	Description
0	No Retrusion	The most anterior portion of the chin is at or near a vertical line drawn from the vermillion border of the lower lip
1	Mild Retrusion	The most anterior portion of the chin is recessed, but less than midway, from a vertical line drawn from the vermillion border of the lower lip.
2	Moderate Retrusion	The most anterior portion of the chin is recessed midway between vertical lines drawn from the vermillion border of the lower lip and the oral commissure.
3	Severe Retrusion	The most anterior portion of the chin is clearly posterior to the midway point between vertical ines drawn from the vermillion border of the lower lip and the oral commissure.

Figure 1: Lines used in the GCRS Descriptors



Secondary effectiveness endpoints included: subjects' satisfaction after treatment with *Restylane® Defyne* versus a no-treatment control using the FACE-Q Satisfaction with Chin scale; comparison of responder rates, using the GCRS, as assessed by the blinded evaluator, at 24, 36, and 48 weeks; aesthetic improvement after treatment with *Restylane® Defyne* compared to no-treatment control using the Global Aesthetic Improvement Scale (GAIS); and Independent Photographic Reviewer (IPR) assessment of improvement in chin retrusion by comparison of random, blinded pairings of the baseline and post-baseline photographs; and volume change over time in the area of the chin as measured by digital 3D photography. Assessment timepoints were measured in weeks after the last injection for the treatment group, or after baseline, if randomized to no treatment. One month was defined as 28 days (4 weeks).

With regard to success/failure criteria, achievement of the primary endpoint was met if the difference between subjects randomized to *Restylane® Defyne* showing an improvement of at least 1 grade from baseline on the GCRS at Week 12, as assessed

by the Blinded Evaluator, was statistically significant when compared with subjects randomized to no treatment. Statistical significance was defined as the two-sided p-value of the comparison of responder rates between the *Restylane® Defyne* treatment group and No treatment group at Week 12 using the Fisher's exact test needed to be smaller than 0.05.

B. Accountability of PMA Cohort

One hundred forty (140) subjects were randomized in the study; 107 subjects were randomized to *Restylane® Defyne*, and 33 subjects were randomized to no treatment. Out of the 107 subjects randomized to treatment, 78 had the touch-up done at Week 4.

As noted below in Table 2, there were 123 subjects that completed the study (i.e., at Week 48 or 12 weeks post optional retreatment, whichever was applicable), and 17 subjects discontinued early. The primary reasons for discontinuation were: lost to follow up (11/140 subjects, 7.9%), and withdrew consent (5/140 subjects, 3.6%). No subject discontinued the study for medical reasons.

At the Week 48 visit, 58.6% (58/99) of subjects in the Restylane Defyne group received re-treatment and 85.2% (23/27) of subjects in the no-treatment group received initial treatment with Restylane Defyne. Of those that did not receive re-treatment or initial treatment, it was due to optimal results being maintained, subject decision, or not meeting eligibility.

Table 2 Summary of Subject Disposition: All Subjects

	Treatment Group		
	Restylane® Defyne **(N=107)**	**No treatment (N = 33)**	**Overall (N = 140)**
Number of Subjects Screened			146
Number of Subjects Randomized	107	33	140
Number of Subjects in the Safety Population	106	33	139
Number of Subjects in the ITT Population	107	33	140
Number of Subjects in the PP Population	99	31	130
Completed the Study	**n (n/N)**	**n (n/N)**	**n (n/N)**
Yes	97 (90.7%)	26 (78.8%)	123 (87.9%)
No	10 (9.3%)	7 (21.2%)	17 (12.1%)

	Treatment Group		
	Restylane® Defyne **(N=107)**	**No treatment (N = 33)**	**Overall (N = 140)**
Reason for Discontinuation			
Withdrew Consent	4 (3.7%)	1 (3.0%)	5 (3.6%)
Lost to Follow-up	6 (5.6%)	5 (15.2%)	11 (7.9%)
Medical Reasons	0	0	0
Other*	0	1 (3.0%)	1 (0.7%)

*withdrew from the study due to moving out of state

The safety population included all subjects who received *Restylane® Defyne* or randomized to no treatment control group based on the as-treated principle.

The ITT population included all subjects who were randomized based on the as-randomized principle.

The per protocol population included all subjects in the ITT population who completed the Week 12 visits without any deviations considered to have a substantial impact on the primary effectiveness outcome.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are presented in Table 3.

Overall most subjects were female (125/140 subjects, 89.3%), of whom 50.4%(63/125) were of childbearing potential. Subjects were predominantly White (107/140 subjects, 76.4%) and not Hispanic or Latino (109/140 subjects, 77.9%); mean age was 47.4 years, and mean BMI was 24.4 kg/m^2. For race, a higher proportion of subjects in the no treatment group were Black or African American (15.2% (5/33) versus 11.2% (12/107)) or 'other' (12.1% (4/33) versus 1.9% (2/107)), although the distribution of Fitzpatrick skin type (FST) categories was similar between the groups. Based on the Blinded Evaluator GCRS baseline score, the *Restylane® Defyne* group had fewer subjects with mild chin retrusion (40/107, 37.4%) and more subjects with moderate chin retrusion (67/107, 62.6%) as compared to the no treatment group (mild chin retursion: 16/33, 48.5%; moderate chin retrusion: 17/33, 51.5%). There were no other notable demographic differences between the subjects randomized to *Restylane® Defyne* and those randomized to no treatment.

This study was designed to enroll an ethnically diverse population by ensuring that out of 140 randomized subjects, at least 21 subjects (21/140 [15%]) would be FST IV–VI, with at least 11 of those subjects with FST V–VI. This goal was met as 57 subjects (57/140 [40.7%]) enrolled in the study were FST IV–VI (43 subjects randomized to *Restylane® Defyne* and 14 subjects randomized to no treatment). Of those 57 subjects, 25 were FST V–VI (19 subjects randomized to *Restylane® Defyne* and 6 subjects randomized to no treatment).

Table 3 Subject Demographics and Baseline Characteristics (Intent to Treat Population)

Characteristic	Statistic	*Restylane® Defyne* (N=107)	No Treatment (N=33)	Overall (N=140)
Age (years)	n	107	33	140
	Mean (SD)	48.3 (12.39)	44.4 (15.30)	47.4 (13.18)
	Median	50.0	44.0	49.5
	Min, Max	20, 70	22, 73	20, 73
Sex, n (%)				
Female	n (%)	95 (88.8)	30 (90.9)	125 (89.3)
Male	n (%)	12 (11.2)	3 (9.1)	15 (10.7)
Height (cm)				
	Mean (SD)	165.14 (8.050)	166.25 (10.963)	165.40 (8.793)
	Median	165.10	165.10	165.10
	Min, Max	149.9, 193.0	142.2, 190.5	142.2, 193.0
Weight (kg)				
	Mean (SD)	66.33 (11.790)	67.49 (9.473)	66.60 (11.265)
	Median	64.85	66.21	65.76
	Min, Max	45.4, 116.1	49.9, 93.0	45.4, 116.1
BMI (kg/m^2)				
	Mean (SD)	24.32 (3.952)	24.59 (3.925)	24.38 (3.933)
	Median	23.62	24.74	23.75
	Min, Max	17.9, 41.3	19.3, 32.5	17.9, 41.3
Race, n (%)				
White	n (%)	85 (79.4%)	22 (66.7%)	107 (76.4%)
Black or African American	n (%)	12 (11.2%)	5 (15.2%)	17 (12.1%)
Asian	n (%)	7 (6.5%)	2 (6.1%)	9 (6.4%)
Native Hawaiian or Other Pacific Islander	n (%)	1 (0.9%)	0	1 (0.7%)
Other	n (%)	2 (1.9%)	4 (12.1%)	6 (4.3%)
Ethnicity, n (%)				
Hispanic or Latino	n (%)	26 (24.3%)	5 (15.2%)	31 (22.1%)
Not Hispanic or Latino	n (%)	81 (75.7%)	28 (84.8%)	109 (77.9%)
Fitzpatrick Skin Types, n (%)				
I	n (%)	7 (6.5%)	1 (3.0%)	8 (5.7%)
II	n (%)	27 (25.2%)	8 (24.2%)	35 (25.0%)
III	n (%)	30 (28.0%)	10 (30.3%)	40 (28.6%)
IV	n (%)	24 (22.4%)	8 (24.2%)	32 (22.9%)
V	n (%)	10 (9.3%)	4 (12.1%)	14 (10.0%)
VI	n (%)	9 (8.4%)	2 (6.1%)	11 (7.9%)
Blinded Evaluator Galderma Chin Retrusion Scale Scores, n (%)				
1: Mild Retrusion	n (%)	40 (37.4%)	16 (48.5%)	56 (40.0%)
2: Moderate Retrusion	n (%)	67 (62.6%)	17 (51.5%)	84 (60.0%)
Treating Investigator Galderma Chin Retrusion Scale Scores, n (%)				

1: Mild Retrusion	n (%)	42 (39.3%)	10 (30.3%)	52 (37.1%)
2: Moderate Retrusion	n (%)	65 (60.7%)	23 (69.7%)	88 (62.9%)

Abbreviations: BMI = body mass index; cm = centimeters; kg = kilograms; max = maximum; min = minimum; SD = standard deviation.

For augmentation and retrusion, the median total volume injected into the chin in the Treatment group was 3.58 mL for the initial and touch-up treatment combined (ranging from 1.0 to 6.0 mL). The median volume injected for retreatment at Week 48 was 2.00 mL (ranging from 0.5 to 4.0 mL).

The no-treatment control group received optional treatment at Week 48. The median total volume for initial treatment in the no treatment group was 2.80 mL (ranging from 0.8 to 4.0 mL).

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 139 subjects available up to the final evaluation (i.e., 12 weeks after retreatment for subjects in the *Restylane® Defyne* treatment group or initial treatment for subjects in the no treatment group), at Week 48. One subject randomized to *Restylane® Defyne* did not complete the baseline visit due to time constraints and did not receive any treatment, the subject was excluded from the safety analysis population and the PP population.

The key safety outcomes for this study are presented below in Tables 4 – 9. Subject reported injection related events are presented in Table 4 - Table 7 Duration of Pre-defined Injection Related Events Occurring in Subjects After Touch-Up Treatment (Safety Population)

Diary Symptom	**Post-Touch-Up Injectionb with *Restylane® Defyne* (N=78) n (%)**				
	Durationa				
	1–3 Days	**4–7 Days**	**8–14 Days**	**15-27 Days**	**28 Daysc**
Pain	32 (41.0)	14 (17.9)	3 (3.8)	0	0
Tenderness	29 (37.2)	23 (29.5)	8 (10.3)	1 (1.3)	1 (1.3)
Redness	28 (35.9)	4 (5.1)	2 (2.6)	0	0
Bruising	8 (10.3)	21 (26.9)	11 (14.1)	0	0
Swelling	25 (32.1)	17 (21.8)	6 (7.7)	1 (1.3)	0
Lumps/Bumps	7 (9.0)	14 (17.9)	9 (11.5)	5 (6.4)	3 (3.8)

Diary Symptom	Post-Touch-Up Injectionb with *Restylane® Defyne* (N=78) n (%)				
	Durationa				
	1–3 Days	4–7 Days	8–14 Days	15-27 Days	28 Daysc
Itching	14 (17.9)	3 (3.8)	3 (3.8)	0	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary. Duration = Number of days with symptoms

[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

[b] Number of subjects who completed at least one diary entry.

[c] Subject diary was only collected for 28 days. Events with a duration of 28 days were ongoing at the end of the subject diary.

. Adverse events (AEs) are presented in Table 9.

Pre-defined Injection Related Events:

Subjects evaluated injection related events (IREs) in a 28-day diary following initial treatment, and touch-up and retreatment, if performed. The presence of pre-defined expected post-treatment events, i.e., pain, tenderness, redness, bruising, swelling, itching, lumps/bumps, and skin discoloration were assessed for the treated area(s). Subjects recorded the presence and level of severity (i.e., none, tolerable, affects daily activities, or disabling) for each of the pre-defined events.

Tenderness, pain, swelling, and lumps/bumps, respectively, were the most commonly reported IREs after initial treatment (112/125 [89.6%]; 92/125 [73.6%]; 92/125 [73.6%]; 88/125 [70.4%] subjects) with *Restylane® Defyne*. Similarly, tenderness, pain, and swelling were commonly reported post touch-up (62/78 [79.5%]; 49/78 [62.8%]; 49/78 [62.8%] subjects) and post-re-treatment (44/58 [75.9%]; 38/58 [65.5%]; 35/58 [60.3%] subjects).

For each treatment period, at least 80% (90/112) of subjects with tenderness, 78% (72/92) of subjects with pain, and 85% (78/92) of subjects with swelling reported it as tolerable.

A total of 6 subjects identified an IRE to be disabling after injection with *Restylane® Defyne*. Pain (including burning) was the most commonly reported disabling IRE (2 subjects [1.6%] post-initial injection and 1 [1.3%] post-touch-up injection); all other IREs (tenderness, lumps/bumps, and bruising) identified as disabling were reported by a single subject each.

For those subjects who experienced pain after treatment with *Restylane® Defyne* it generally lasted between 1-3 days (initial [55/92 subjects; 60%], touch-up [32/49 subjects; 65%], re-treatment [19/38 subjects; 50%]. Of the subjects who experienced tenderness it tended to last between 1–7 days after injections (initial [75/112 subjects;

67%], touch-up [52/62 subjects; 84%], and re-treatment [30/44 subjects; 68%]) with investigational treatment. Of the subjects who experienced swelling it also tended to last between 1–7 days after injections (initial [84/92 subjects; 91%], touch-up [42/49 subjects; 86%], and re-treatment [27/35 subjects; 77%]) with *Restylane® Defyne*.

Lumps/bumps was the IRE most frequently reported by subjects to last longer than 14 days after injections with *Restylane® Defyne* (initial [26/88 subjects; 30%]), touch-up [8/38 subjects; 21%], and re-treatment [11/34 subjects; 32%]).

Subjects typically reported IREs at a lower incident rate, lower severity, and shorter duration following touch-up and re-treatment, when compared to initial treatment.

Table 4 Pre-defined Injection Related Events by Maximum Severity Occurring in Subjects After Initial Treatment (Safety Population)

	Post Initial Injection with *Restylane® Defyne* (N=125) n (%)			
Diary Symptoms	**Total % (n/N)[a]**	**Tolerable %**	**Affects Daily Activities %**	**Disabling %**
Any Symptom	92.8 (116/125)	71.6 (83/116)	25.9 (30/116)	2.6 (3/116)
Pain (including burning)	79.3 (92/116)	78.3 (72/92)	19.6 (18/92)	2.2 (2/92)
Tenderness	96.6 (112/116)	80.4 (90/112)	18.8 (21/112)	0.9 (1/112)
Redness	55.2 (64/116)	89.1 (57/64)	10.9 (7/64)	0
Bruising	73.2 (85/116)	80.0 (68/85)	20.0% (17/85)	0
Swelling	79.3 (92/116)	84.8 (78/92)	15.2 (14/92)	0
Lumps/bumps	75.9 (88/116)	90.9 (80/88)	9.1 (8/88)	0
Itching	33.6 (39/116)	92.3 (36/39)	7.7 (3/39)	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary.
[a] Number of subjects who completed at least one diary entry.

Table 5 Pre-defined Injection Related Events by Maximum Severity Occurring in Subjects After Re-treatment (Safety Population)

Diary Symptoms	Post Re-treatment Injection with *Restylane® Defyne* (N=58) n (%)			
	Total % (n/N)[a]	**Tolerable %**	**Affects Daily Activities %**	**Disabling %**
Any Symptom	75.9 (44/58)	81.8 (36/44)	13.6 (6/44)	4.5 (2/44)
Pain (including burning)	86.4 (38/44)	86.8 (33/38)	13.2 (5/38)	0
Tenderness	100.0 (44/44)	90.9 (40/44)	9.1 (4/44)	0
Redness	54.5 (24/44)	95.8 (23/24)	4.2 (1/24)	0
Bruising	72.3 (32/44)	93.8 (30/32)	3.1 (1/32)	3.1 (1/32)
Swelling	79.5 (35/44)	88.6 (31/35)	11.4 (4/35)	0
Lumps/bumps	77.3 (34/44)	85.3 (29/34)	11.8 (4/34)	2.9 (1/34)
Itching	27.3 (12/44)	100.0 (12/12)	0	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary.
[a] Number of subjects who completed at least one diary entry.

Table 6 Duration of Pre-defined Injection Related Events Occurring in Subjects After Initial Treatment (Safety Population)

Diary Symptom	Post-Initial Injection[b] with *Restylane® Defyne* (N=125) n (%)				
	Duration[a]				
	1–3 Days	**4–7 Days**	**8–14 Days**	**15-27 Days**	**28 Days[c]**
Pain	55 (44.0)	27 (21.6)	8 (6.4)	1 (0.8)	1 (0.8)
Tenderness	35 (28.0)	40 (32.0)	31 (24.8)	4 (3.2)	2 (1.6)
Redness	47 (37.6)	8 (6.4)	7 (5.6)	2 (1.6)	0
Bruising	11 (8.8)	39 (31.2)	32 (25.6)	3 (2.4)	0
Swelling	52 (41.6)	32 (25.6)	4 (3.2)	3 (2.4)	1 (0.8)
Lumps/Bumps	20 (16.0)	20 (16.0)	22 (17.6)	17 (13.6)	9 (7.2)

Diary Symptom	Post-Initial Injection[b] with *Restylane® Defyne* (N=125) n (%)				
	Duration[a]				
	1–3 Days	4–7 Days	8–14 Days	15-27 Days	28 Days[c]
Itching	27 (21.6)	5 (4.0)	3 (2.4)	4 (3.2)	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary. Duration = Number of days with symptoms

[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

[b] Number of subjects who completed at least one diary entry.

[c] Subject diary was only collected for 28 days. Events with a duration of 28 days were ongoing at the end of the subject diary.

Table 7 Duration of Pre-defined Injection Related Events Occurring in Subjects After Touch-Up Treatment (Safety Population)

Diary Symptom	Post-Touch-Up Injection[b] with *Restylane® Defyne* (N=78) n (%)				
	Duration[a]				
	1–3 Days	4–7 Days	8–14 Days	15-27 Days	28 Days[c]
Pain	32 (41.0)	14 (17.9)	3 (3.8)	0	0
Tenderness	29 (37.2)	23 (29.5)	8 (10.3)	1 (1.3)	1 (1.3)
Redness	28 (35.9)	4 (5.1)	2 (2.6)	0	0
Bruising	8 (10.3)	21 (26.9)	11 (14.1)	0	0
Swelling	25 (32.1)	17 (21.8)	6 (7.7)	1 (1.3)	0
Lumps/Bumps	7 (9.0)	14 (17.9)	9 (11.5)	5 (6.4)	3 (3.8)
Itching	14 (17.9)	3 (3.8)	3 (3.8)	0	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary. Duration = Number of days with symptoms

[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

[b] Number of subjects who completed at least one diary entry.

[c] Subject diary was only collected for 28 days. Events with a duration of 28 days were ongoing at the end of the subject diary.

Table 8 Duration of Pre-defined Injection Related Events Occurring in Subjects After Re-treatment (Safety Population)

Diary Symptom	Post-Re-treatment Injection[b] with *Restylane® Defyne* (N=58) n (%)				
	Duration[a]				
	1–3 Days	4–7 Days	8–14 Days	15-27Days	28 Days[c]
Pain (including burning)	19 (32.8)	16 (27.6)	2 (3.4)	1 (1.7)	0
Tenderness	13 (22.4)	17 (29.3)	12 (20.7)	2 (3.4)	0
Redness	14 (24.1)	7 (12.1)	2 (3.4)	1 (1.7)	0
Bruising	7 (12.1)	12 (20.7)	12 (20.7)	1 (1.7)	0
Swelling	11 (19.0)	16 (27.6)	8 (13.8)	0	0
Lumps/Bumps	4 (6.9)	8 (13.8)	11 (19.0)	5 (8.6)	6 (10.3)
Itching	6 (10.3)	5 (8.6)	1 (1.7)	0	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary. Duration = Number of days with symptoms

[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

[b] Number of subjects who completed at least one diary entry.

[c] Subject diary was only collected for 28 days. Events with a duration of 28 days were ongoing at the end of the subject diary.

Device and Injection Related Events: AEs were evaluated by Investigators throughout entirety of the study. An overall summary of AEs following initial and touch-up treatment is presented in Table 9.

The majority of subjects reported no AEs across all treatment periods (no treatment at baseline [27/33, 81.8%]; initial treatment [88/129, 68.2%]; re-treatment [54/58, 93.1%]). Overall, 51 subjects reported a total of 81 AEs across all treatment periods (no treatment at baseline [6/33, 18.2%]; initial treatment [41/129, 31.8%]; re-treatment [4/58, 6.9%]). All of the 81 AEs reported were classified as either mild (62/81 [76.5%]) or moderate (19/81 [23.5%]); no severe AEs were reported during the study. There was one SAE during the study experienced by 1 (0.8%) subject that was not related the investigational treatment or procedure (stage IV metastatic lung cancer).

A total of 25 AEs were related to the investigational treatment or injection procedure and were reported either after initial treatment (18/129 [14.0%]) or re-treatment (1/58 [1.7%]) with *Restylane® Defyne*.

In terms of onset time, the median onset for related AEs was at the day of treatment with *Restylane® Defyne* (mean, 11.5 days). One subject experienced delayed implant site swelling in the chin of mild severity 185 days after initial treatment with *Restylane® Defyne* that lasted 4 days and resolved following treatment.

There were no ongoing AEs at the end of the study. After treatment with *Restylane® Defyne*, most related AEs resolved within approximately a week (8 days).

The severity and duration of treatment related AEs occurring in <5% of subjects in either treatment group are summarized in Table 10 - Chin function and sensation evaluations for all subjects at all visits were assessed as normal. For device palpability, at least 95.5% of subjects had normal (expected feel) of the chin following treatment with *Restylane® Defyne*.

Table 9 Summary of Adverse Events After Initial/Re-treatment (Safety Population)

	Initial Treatment with *Restylane® Defyne* (N=129)		**Re-treatment with *Restylane® Defyne* (N=58)**	
	Subjects n (%)	**Events**	**Subjects n (%)**	**Events**
AEs Overall	47 (36.4)	77	4 (6.9)	4
Any AE Related to Study Product or Injection Procedure				
Total	18 (14.0)	24	1 (1.7)	1
Mild	17 (94.4)	23	1 (100)	1
Moderate	1 (5.6)	1	0	0
Severe	0	0	0	0
Action Required				
None	8 (44.4)	12	0	0
Medication	10 (55.6)	12	1(100)	1
Non-Pharmacological	1 (5.6)	1	0	0
Withdrawal	0	0	0	0
Mean Onset of Related AEs (days)	11.5	24	0.0	1
Minimum	0	--	0	--
Maximum	185	--	0	--
Mean Duration of Related AEs (days)	13.1	24	4.0	1
Minimum	2	--	4	--
Maximum	112	--	4	--
Unrelated AEs to Study Product or Injection Procedures	29 (22.5)	47	3 (5.2)	3
Serious AEs (not related to the study product or injection procedure)	1 (0.8)	1	0	0
No AEs	88 (68.2)	--	54 (93.1)	--

Table 10 Treatment Related Adverse Events Occurring <5% of Subjects by Maximum Severity after Initial/Re-treatment (Safety Population)

	Initial Treatment with *Restylane Defyne* (N=129)				Re-treatment with *Restylane Defyne* (N=58)			
Adverse Event	**Subjects n (%)**	**Mild %**	**Moderate %**	**Severe %**	**Subjects n (%)**	**Mild %**	**Moderate %**	**Severe %**
Implant site pain	6 (4.7)	5 (83.3)	1 (16.7)	0	1	1 (1.7)	0	0
Implant site bruising	3 (2.3)	3 (100)	0	0	0	0	0	0
Implant site swelling	3 (2.3)	3 (100)	0	0	0	0	0	0
Implant site erythema	2 (1.6)	2 (100)	0	0	0	0	0	0
Implant site haemorrhage	2 (1.6)	2 (100)	0	0	0	0	0	0
Implant site nodule	2 (1.6)	2 (100)	0	0	0	0	0	0
Implant site mass	1 (0.8)	1 (100)	0	0	0	0	0	0
Implant site oedema	1 (0.8)	1 (100)	0	0	0	0	0	0
Injection site eczema	1 (0.8)	1 (100)	0	0	0	0	0	0
Oral Herpes	1 (0.8)	1 (100)	0	0	0	0	0	0

Table is sorted in descending order by overall incidence rate.

Chin and Lower Lip Safety Assessments: Chin and lower lip sensation, lip movement, function, mass formation, and product palpability were performed at screening/baseline and all physical visits thereafter. The parameters for lip movement, function, mass formation and product palpability were rated as normal or abnormal. Lip function was graded separately from Chin function.

In the study, chin function and sensation evaluations for all subjects at all visits were assessed as normal. For device palpability, at least 95.5% of subjects had normal (expected feel) of the chin following treatment with *Restylane® Defyne*.

Additional Safety Assessments: Changes in hair growth in the treated area for male subjects were evaluated at physical follow-ups after baseline treatment; any changes were to be reported as AEs. There were no changes in hair growth assessed in male subjects for this study.

Exploratory Subgroup Analyses: Exploratory safety analyses by subgroup (i.e., gender, study site, median injection volume of ≤ 2.7 mL and > 2.7 mL, and FST) were evaluated. Some of the subgroup analyses of treatment-related AEs occurring in subjects after initial and re-treatment with *Restylane® Defyne* are summarized in Table 10.

A total of 7 of 11 study sites had subjects who experienced related AEs. The variability between sites (0-54%) may be explained by the relatively small sample size at each site.

This study stratified subjects by FST group (I-III, IV, or V-VI). There were no marked differences in proportion of subjects who experienced at least one related AE based on FST group, 12% vs. 16.7% vs. 16.7% for FST I-–III vs. IV vs. V-–VI skin types, respectively, in the initial treatment with *Restylane® Defyne* group. One subject (1/14 [7.1%]) who received a re-treatment with *Restylane® Defyne,* with FST IV, experienced at least one related AE.

Table 10 Incidence of Related AEs after Initial/Re-treatment by Subgroup

Category	Initial Treatment with *Restylane® Defyne* % (N=129)	Re-treatment with *Restylane® Defyne* (N=58)
Gender		
Female	14.8 (17/115)	2.0 (1/51)
Male	7.1 (1/14)	0
Age Group		
20-29 years	21.4 (3/14)	0 (0/5)
30-50 years	19.2 (10/52)	0 (0/19)
>50 years	7.9 (5/63)	2.9 (1/34)
Median Injection Volume		
≤ 2.7 mL	13.8 (9/65)	0
>2.7 mL	14.1(9/64)	2.8 (1/36)
FST		
FST I-III	12.0 (9/75)	0
FST IV	16.7 (6/30)	7.1 (1/14)
FST V-VI	16.7 (4/24)	0

2. Effectiveness Results

The analysis of effectiveness was based on the cohort of 130 subjects available up to the Week 48 evaluation. A total of 9 subjects (7 randomized to *Restylane® Defyne*, and 2 subjects randomized to no treatment) were excluded from the per protocol analysis population due to deviations considered to have substantial impact on the primary effectiveness outcome. Key effectiveness outcomes are presented in Table 11 - Table 12.

Primary Endpoint: The investigator rated the subject's chin area for severity of retrusion using the 4-point GCRS. Scoring was based on a visual live assessment at defined time points, and not in comparison to the baseline appearance. A responder was defined as at least a one point improvement from the baseline GCRS score. Sensitivity analyses of the primary endpoint using the PP population and ITT population without imputation (i.e., observed cases only) also showed statistically significant improvements in responder rates in favor of *Restylane® Defyne.* The proportion of responders at Week 12 is presented in Table 11.

Table 11 Responder Rates using the GCRS as Assessed by Blinded Evaluator at Week 12: Sensitivity Analyses (PP and ITT Population [Observed Cases Only)

Population (Imputation) Category	Statistic	*Restylane® Defyne*	No Treatment	Difference	P-Value
PP Population		**N=99**	**N=31**		
At Least 1-Grade Improvement	m/n (%)	85/99 (85.9%)	2/31 (6.5%)	(79.4%)	<0.001
	95% CI	(77.41, 92.05)	(0.79, 21.42)	(66.25, 92.57)	
0: No Retrusion	m/n (%)	46/99 (46.5%)	0/31		
1: Mild Retrusion	m/n (%)	49/99 (49.5%)	16/31 (51.6%)		
2: Moderate Retrusion	m/n (%)	4/99 (4.0%)	15/31 (48.4%)		
3: Severe Retrusion	m/n (%)	0/99	0/31		
ITT Population		**N=107**	**N=33**		
At Least 1-Grade Improvement	m/n (%)	87/101 (86.1%)	2/31 (6.5%)	(79.7%)	<0.001
	95% CI	(77.84, 92.21)	(0.79, 21.42)	(66.62, 92.76)	
0: No Retrusion	m/n (%)	47/101 (46.5%)	0/31		
1: Mild Retrusion	m/n (%)	50/101 (49.5%)	16/31 (51.6%)		
2: Moderate Retrusion	m/n (%)	4/101 (4.0%)	15/31 (48.4%)		
3: Severe Retrusion	m/n (%)	0/101	0/31		

Secondary Effectiveness Analyses: The following secondary endpoints were evaluated to assess secondary effectiveness.

Blinded Evaluator GCRS, Over Time:

Further to the statistically significant improvement from baseline to Week 12, a significantly greater proportion of *Restylane® Defyne* subjects achieved a 1-grade or greater improvement in GCRS, compared with no treatment, at Weeks 24, 36 and 48, as shown in Table 12.

Table 12 Responder Rates using the GCRS as Assessed by Blinded Evaluator at Each Visit: Observed Cases (ITT Population)

Visit	Statistic	*Restylane® Defyne* [N=107]	No Treatment [N=33]	Difference
Visit 6 (Week 12)	m/n (%)	87/101 (86.1%)	2/31 (6.5%)	(79.7%)
	95% CI	(77.84, 92.21)	(0.79, 21.42)	(66.62, 92.76)
Visit 7 (Week 24)	m/n (%)	84/98 (85.7%)	2/30 (6.7%)	(79.0%)
	95% CI	(77.19, 91.96)	(0.82, 22.07)	(65.57, 92.52)
Visit 8 (Week 36)	m/n (%)	76/98 (77.6%)	5/26 (19.2%)	(58.3%)
	95% CI	(68.01, 85.36)	(6.55, 39.35)	(38.63, 78.01)
Visit 9 (Week 48)	m/n (%)	73/99 (73.7%)	3/27 (11.1%)	(62.6%)
	95% CI	(63.93, 82.07)	(2.35, 29.16)	(45.58, 79.67)

Subject FACE-Q Questionnaire, Satisfaction with Chin:

The FACE-Q questionnaire was used to assess treatment outcome from the subject's perspective at baseline, 12, 24, 36, and 48 weeks after randomization.

At Week 12, mean total scores were similar between the treatment groups at baseline (37.4 [*Restylane® Defyne*] versus 34.6 [no treatment] on the 100-point scale). At Week 12, the mean total score was 78.6 for the *Restylane® Defyne* group, and 35.1 for the no treatment group. The treatment difference in favor of *Restylane® Defyne* was statistically significant.

Subjects who were treated with *Restylane® Defyne* reported greater satisfaction with the appearance of their chin, compared with no treatment, based on mean Rasch transformed FACE-Q total scores at Week 12 (Difference between the means 40.7; 95% CI: 33.7, 47.8; $p<0.001$); sensitivity and subgroup analyses confirmed the robustness of the primary analysis. The durability of the treatment response extended to the later assessments with change from baseline in Rasch transformed FACE-Q total scores consistently greater in the *Restylane® Defyne* group compared with no treatment (Week 24 [38.4 versus -1.4], Week 36 [31.2 versus -4.1] and Week 48 [24.5 versus -2.3]), where higher scores indicate greater satisfaction on the 0–100 scale.

Subject and Treating Investigator GAIS:

Independently of each other, the investigator and the subject evaluated the degree of improvement from baseline in the appearance of the subject's chin area using the

GAIS at each post-baseline visit. The proportion of subjects who reported aesthetic improvements (improved, much improved or very much improved) in the chin area across the Week 12, Week 24, Week 36 and Week 48 assessments using the GAIS was substantially higher in the *Restylane® Defyne* group (84.8–99.0%), compared with the no treatment group (0–3.7%). Similarly, across the same time points, Treating Investigators scored 96.0–100% of subjects in the *Restylane® Defyne* group as improved, compared with 0–3.3% of subjects in the no treatment group.

Exploratory Subgroup Analyses

The exploratory effectiveness analyses by subgroup (i.e., gender, age, injection volume, FST, race and ethnicity) demonstrated that the results at Week 12 were consistent with the primary analysis based on the difference of means in the GCRS (no treatment control minus *Restylane® Defyne*). Results for the exploratory effectiveness analyses are summarized in Table 13.

Table 13 Responder Rates by Gender, FST, Race and Ethnicity using the GCRS as Assessed by Blinded Evaluator at Week 12: Observed Cases (ITT Population)

Category	Statistic	*Restylane® Defyne* [N=107]	No Treatment [N=33]	Difference
Gender				
Female	m/n (%)	77/95 (81.1%)	2/30 (6.7%)	(74.4%)
	95% CI	(71.72, 88.37)	(0.82, 22.07)	(60.29, 88.49)
Male	m/n (%)	10/12 (83.3%)	0/3	(83.3%)
	95% CI	(51.59, 97.91)	(0.00, 70.76)	(41.41, 100.00)
Age				
20-29 years	m/n (%)	8/9 (88.9%)	18/ (12.5%)	(76.4%)
	95% CI	(51.75, 99.72)	(0.32, 52.65)	(33.81, 100.00)
30-50 years	m/n (%)	37/45 (82.2%)	1/12 (8.3%)	(73.9%)
	95% CI	(67.95, 92.00)	(0.21, 38.48)	(49.39, 98.38)
> 50 years	m/n (%)	42/53 (79.2%)	0/13 (0.00%)	(79.2%)
	95% CI	(65.89, 89.16)	(0.00, 24.71)	(63.54, 94.95)
Median Injection Volume				
≤ 2.7mL	m/n (%)	41/49 (83.7%)	1/16 (6.3%)	(77.4%)
	95% CI	(70.34, 92.68)	(0.16, 30.23)	(57.54, 97.31)
> 2.7 mL	m/n (%)	46/57 (80.7%)	0/7 (0.00%)	(80.7%)
	95% CI	(68.09, 89.95)	(0.00, 40.96)	(62.44, 98.97)
FST				
FST I-III	m/n (%)	51/64 (79.7%)	2/19 (10.5%)	(69.2%)
	95% CI	(67.77, 88.72)	(1.30, 33.14)	(48.79, 89.53)
FST IV	m/n (%)	21/24 (87.5%)	0/8	(87.5%)

Category	Statistic	*Restylane® Defyne* [N=107]	No Treatment [N=33]	Difference
	95% CI	(67.64, 97.34)	(0.00, 36.94)	(65.94, 100.00)
FST V-VI	m/n (%)	15/19 (78.9%)	0/6	(78.9%)
	95% CI	(54.43, 93.95)	(0.00, 45.93)	(49.65, 100.00)
Race				
White	m/n (%)	71/85 (83.5%)	2/22 (9.1%)	(74.4%)
	95% CI	(73.91, 90.69)	(1.12, 29.16)	(57.21, 91.67)
Black	m/n (%)	9/12 (75.0%)	0/5	(75.0%)
	95% CI	(42.81, 94.51)	(0.00, 52.18)	(36.33, 100.00)
Other Races	m/n (%)	7/10 (70.0%)	0/6	(70.0%)
	95% CI	(34.75, 93.33)	(0.00, 45.93)	(28.26, 100.00)
Ethnicity				
Hispanic	m/n (%)	20/26 (76.9%)	0/5	(76.9%)
	95% CI	(56.35, 91.03)	(0.00, 52.18)	(48.81, 100.00)
Non-Hispanic	m/n (%)	67/81 (82.7%)	2/28 (7.1%)	(75.6%)
	95% CI	(72.70, 90.22)	(0.88, 23.50)	(60.57, 90.58)

E. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

F. Financial Disclosure

The Financial Disclosure by clinical investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation.

The clinical study included 11 investigators, two (2) of whom had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). These two investigators had disclosable financial interests/arrangements described as significant payment of other sorts. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and

Plastic Surgery Devices Advisory Panel, an FDA advisory committee, for review and recommendation.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of the US pivotal study. Conclusions drawn from clinical study provide a reasonable assurance that the device is effective when used for augmentation of the chin region to improve the chin profile in subjects over the age of 21.

Conclusions from this study are:

- The primary endpoint of the study was met. A total of 87 (81.3%) subjects randomized to *Restylane® Defyne* achieved an improvement of at least 1 grade from baseline on the GCRS at Week 12, assessed by the Blinded Evaluator, compared with 2 (6.1%) subjects randomized to no treatment (Difference 75.2%; 95% CI: 62.27, 88.22; $p<0.001$). Sensitivity and subgroup analyses confirmed the robustness of the primary analysis.

- Significantly greater proportions of *Restylane® Defyne* subjects achieved a 1-grade or greater improvement in GCRS, compared with no treatment, at all timepoints (Week 24, Week 36 and Week 48) based on Blinded Evaluator assessments ($p<0.001$ in all cases).

- Subjects who were treated with *Restylane® Defyne* reported greater satisfaction with the appearance of their chin based on FACE-Q scores at Week 12, compared with no treatment The durability of the treatment response extended to the later assessments with change from baseline scores consistently greater in the *Restylane® Defyne* group compared with no treatment (Week 24, Week 36, and Week 48).

- The proportion of subjects who reported aesthetic improvements (improved, much improved or very much improved) in the chin area across the Week 12, Week 24, Week 36 and Week 48 assessments using the GAIS was substantially higher in the *Restylane® Defyne* group (84.8–99.0%), compared with the no treatment group (0–3.7%); Treating Investigators scored 96.0–100% of subjects in the *Restylane® Defyne* group as improved, compared with 0–3.3% of subjects in the no treatment group.

B. Safety Conclusions

Assessment of product safety is based on the results of the US pivotal study.

Conclusions from this study are:

- The majority of subjects reported pre-defined IREs in subject diaries. The most commonly reported IREs after initial treatment with *Restylane® Defyne* were tenderness (89.6%), pain (73.6%), swelling (73.6%), and lumps/bumps (70.4%). A similar reporting pattern was observed after touch-up at 4 weeks and re-treatment at Week 48. The majority of IREs were considered tolerable and typically lasted for 14 days or less.

- The majority of subjects who either received no treatment at baseline (27/33 [81.8%]), initial treatment (88/129 [68.2%]), or re-treatment (54/58 [93.1%]) with *Restylane® Defyne* did not experience AEs.

- A total of 18 subjects (18/129 [14.0%]) reported related AEs during the initial treatment period and 1 subject (1/58 [1.7%]) reported a related AE after the re-treatment with *Restylane® Defyne.* The most frequently reported investigational treatment or injection procedure-related AEs after initial treatment with *Restylane® Defyne* were implant site pain (6/129 [4.7%]), implant site bruising (3/129 [2.3%]), and implant site swelling (3/129 [2.3%]).

- The majority of related AEs (24/25) were of mild severity; one subject reported implant site pain of moderate severity.

- Most subjects experienced the onset of related AEs typically on the day of investigational treatment (i.e., median time to onset was 0 days) both following initial treatment and re-treatment with *Restylane® Defyne*; however, two subjects experienced late-onset AEs, more than 21 days after initial treatment (53 days and 185 days after their treatment).

- The median duration of AEs related to treatment or injection procedure was 4.0 days, ranging from 2 to 112 days after initial treatment with *Restylane® Defyne*. All events were resolved at study end.

- Subgroup analysis revealed that exploratory safety analyses by subgroup (i.e., study site, injection volume, and FST) were consistent with the AE data overall. One SAE unrelated to investigational treatment or injection procedure (metastatic lung cancer, stage IV) was reported.

- Over 95% of subjects were assessed to have a normal expected feel upon palpation of the chin after treatment with *Restylane® Defyne* throughout the study.

- In 3 subjects (3/129 [2.3%]) assessment of mass formation was positive after initial treatment with *Restylane® Defyne*. The mass formations all resolved and were no longer detectable within one or two visits from initial identification.

- All subjects displayed normal lower lip function, sensation, and movement. All subjects displayed normal chin function and sensation.

C. Benefit-Risk Conclusions

The primary potential benefit of the device is a perceived improvement in the visual appearance of chin retrusion as assessed by the investigator using the GCRS, improved global aesthetic appearance according to investigator and subject GAIS assessments, and subject satisfaction with treatment per the FACE-Q questionnaire.

The risks associated with chin augmentation of the chin region to improve the chin profile using *Restylane® Defyne* primarily include injection site reactions (e.g., tenderness). Most of the pre-defined, expected post-treatment events were tolerable in severity, and resolved in 14 days or less.

1. Patient Perspectives

   Patient perspectives considered during the review included:

   - FACE-Q Questionaires (to assess patient satisfaction with chin). Results for FACE-Q are discussed in Sectinon X.D.2 of this memo.
   - GAIS assessed by the patients at 12, 24, 36, and 48 weeks. Results for GAIS assessments are discussed in Sectinon X.D.2 of this memo
   - Adverse events were obtained from signs and symptoms reported by patients during visits. Adverse events that were reporteted during the study are summarized in Tables 9 and 10.
   - Diaries, which were completed by patients for 4 weeks after each treatment, were used to collect information about predefined, injection related events at the treated area.
   - Table 2 shows the disposition of patient and the reasons why patienst discontinued from the study.

In conclusion, given the available information above, the data support that for augmentation of the chin region to improve the chin profile in patients with mild to moderate chin retrusion over the age of 21 the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on January 29, 2021.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.